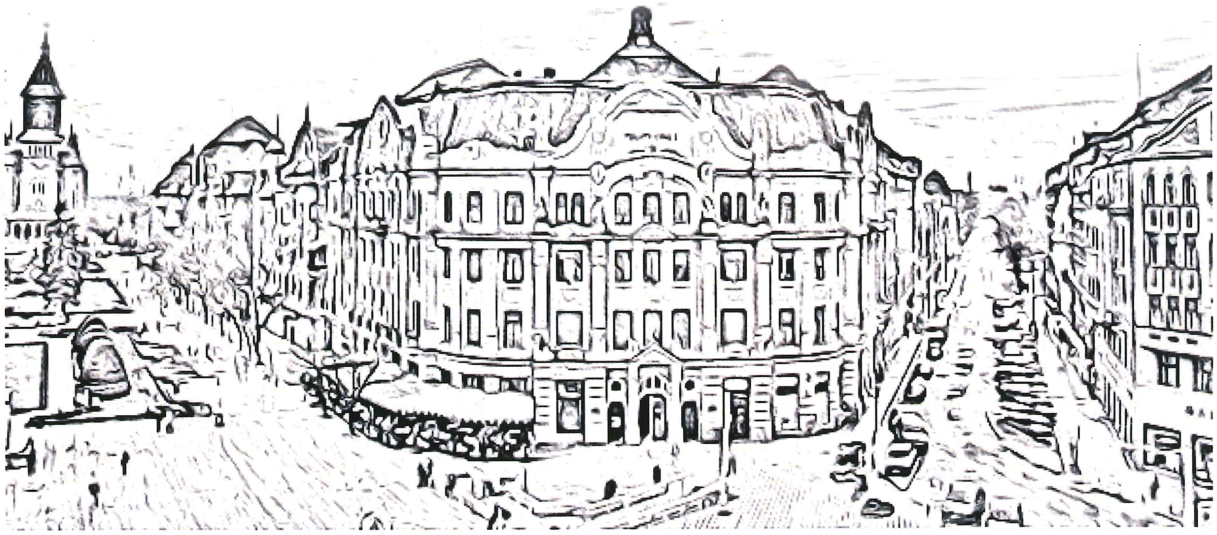
CEUM

2017

19th Central and Eastern European NMR Symposium & Bruker Users' Meeting 5-8th of September, Timișoara, Romania

Book of Abstracts



P17. PHOSPHATE ESTER BOND HYDROLYSIS PROMOTED BY LANTHANIDE-SUBSTITUTED KEGGIN TYPE POLYOXOMETALATES STUDIED BY 1D, 2D NMR SPECTROSCOPY AND DENSITY FUNCTIONAL THEORY APPROACH

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Hydrolytic cleavage of 4-nitrophenyl phosphate (NPP), a commonly used DNA model substrate, was examined in the presence of series of lanthanide-substituted Keggin type polyoxometalates (POMs) $[Me_2NH_2]11[Ce^{III}(PW_{11}O_{39})_2]$, $[Me_2NH_2]_{10}[Ce^{IV}(PW_{11}O_{39})_2]$ (abbreviated as $(Ce^{IV}(PW_{11})_2)$ and $K_4[EuPW_{11}O_{39}]$ by means of NMR, luminescence spectroscopy and DFT calculations. Among the examined complexes, $Ce^{IV}(PW_{11})_2$ showed the highest reactivity, and its aqueous speciation was fully determined under different conditions (pD, temperature, etc.) by means of ^{31}P and ^{31}P Diffusion Ordered NMR Spectroscopy (DOSY). The cleavage of the phosphoester bond of NPP in the presence of $(Ce^{IV}(PW_{11})_2)$ was studied by ^1H and ^{31}P NMR spectroscopy, proceeded with an observed rate constant, $k_{obs} = 5.31 \times 10^{-6}$ s^{-1} at pD 6.4 and 50 °C. The pD dependence of NPP hydrolysis exhibits a bell-shaped profile, with the fastest rate observed at pD 6.4. The formation constant ($K_f = 127$ M^{-1}) and catalytic rate constant ($k_c = 19.41 \times 10^{-5}$ s^{-1}) for the NPP-Ce(IV)-Keggin POM complex were calculated and binding between $Ce^{IV}(PW_{11})_2$ and the phosphate group of NPP was also evidenced by the change of the chemical shift of the ^{31}P nucleus in NPP upon addition of the POM complex. DFT calculations revealed that binding of NPP to the parent catalyst $Ce^{IV}(PW_{11})_2$ is thermodynamically unlikely. On the contrary, formation of complexes with the monomeric 1:1 species, $Ce^{IV}PW_{11}$, is considered to be more favourable and the most stable complex, $[Ce^{IV}PW_{11}(H_2O)_2(NPP\text{-}\kappa O)_2]^{7-}$, was found to involve two NPP ligands coordinated to the Ce^{IV} center of $Ce^{IV}PW_{11}$ in the monodentate fashion. Based on these findings a principle mechanism for the hydrolysis of NPP by the POM is proposed.[1]

[1] T. K. N. Luong, T. T. Mihaylov, G. Absillis, P. Shestakova, K. Pierloot, and T. N. Parac-Vogt, Phosphate Ester Bond Hydrolysis Promoted by Lanthanide-Substituted Keggin-type Polyoxometalates Studied by a Combined Experimental and Density Functional Theory Approach, Inorg. Chem. 55 (2016), 9898-9911.

Phosphate Ester Bond Hydrolysis Promoted by Lanthanide-substituted Keggin Type Polyoxometalates Studied by 1D, 2D NMR Spectroscopy and Density Functional Theory Approach

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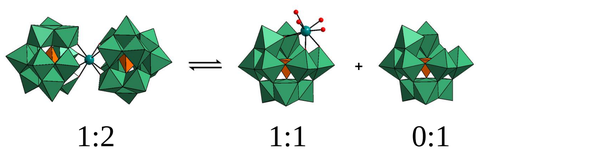
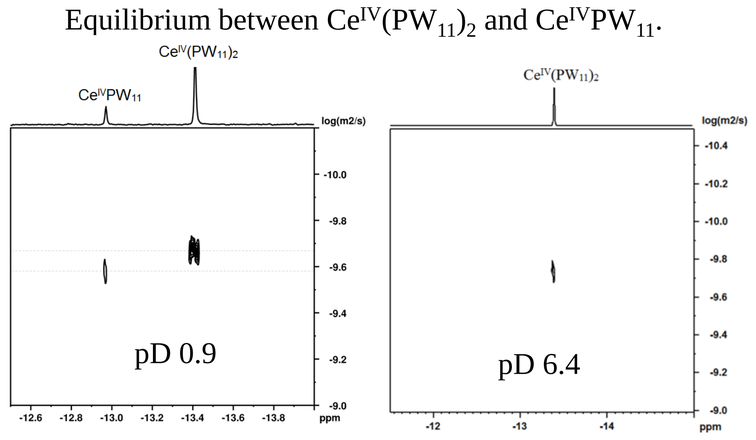
Introduction

Polyoxometalates (POMs) are oxygen anion clusters formed by early transition metals (M = V, Nb, Ta, Mo and W) in their highest oxidation state. Several classes of POMs have been reported to have potent anti-tumor, anti-viral and anti-bacterial properties, resulting in a substantial interest in the potential medicinal application of POMs. We have previously discovered that a Ce^{IV}-substituted Keggin POM $[Me_2NH_2]_{11}[Ce^{IV}(PW_{11}O_{39})_2]$, abbreviated as $(Ce^{IV}(PW_{11})_2)$, in which the Keggin moiety was used as a chelating agent for Ce^{IV}, promotes selective peptide bond hydrolysis of hen egg-white lysozyme at physiological pH and temperature and therefore can be regarded as artificial metalloprotease that operates under mild conditions.[1] In this study we further explore the phosphoesterase activity of $Ce^{IV}(PW_{11})_2$ towards 4-nitrophenyl phosphate (NPP) hydrolysis by means of ^1H and ^{31}P NMR spectroscopy. Aqueous speciation of $Ce^{IV}(PW_{11})_2$ was fully determined under different conditions of pD, temperature, concentration, and ionic strength by means of ^{31}P and ^{31}P Diffusion-Ordered NMR SpectroscopY (DOSY). The binding properties of NPP to $Ce^{IV}(PW_{11})_2$ and to its dissociation product $Ce^{IV}PW_{11}$ were theoretically investigated by means of density functional theory (DFT). A detailed kinetic study by multinuclear NMR measurements combined with DFT calculation allowed to propose the detailed mechanism of NPP hydrolysis catalyzed by this POM.[2,3]

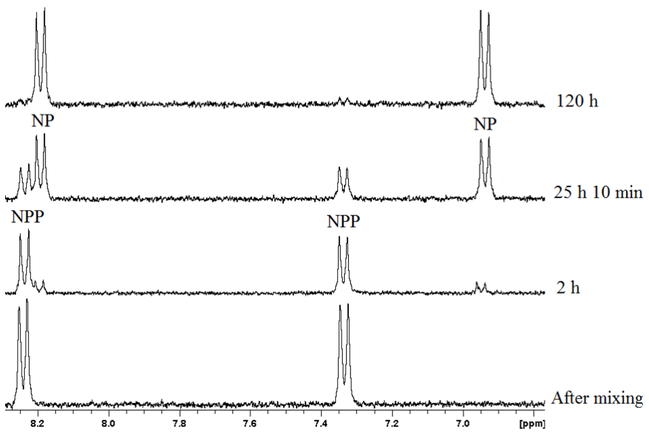
Results and discussion



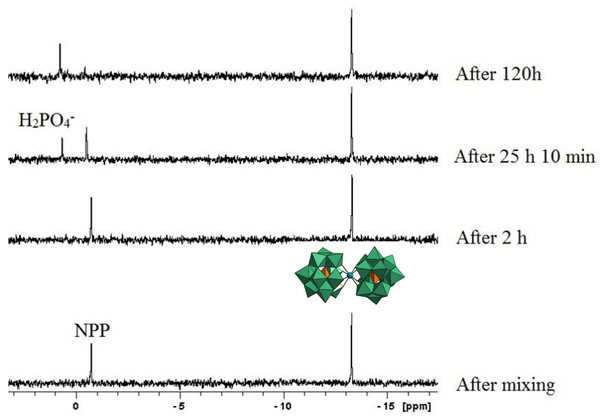
Equilibrium between $Ce^{IV}(PW_{11})_2$ and $Ce^{IV}PW_{11}$.



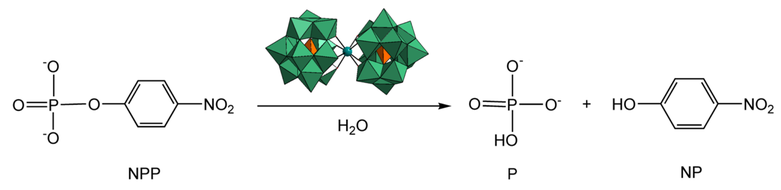
^{31}P DOSY spectrum of 6.0 mM $Ce^{IV}(PW_{11})_2$ at pD 0.9 and pD 6.4.



^1H spectra of 1.0 mM of NPP and 1.0 mM of $Ce^{IV}(PW_{11})_2$ at different time intervals at pD 6.4 and 50 °C.

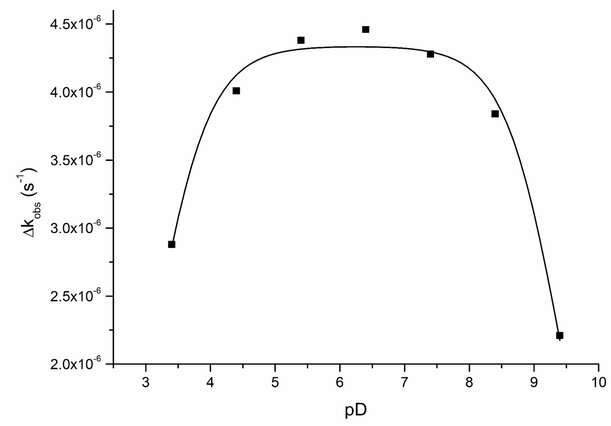


^{31}P spectra of 1.0 mM of NPP and 1.0 mM of $Ce^{IV}(PW_{11})_2$ at different time intervals at pD 6.4 and 50 °C.



Hydrolysis of NPP promoted by $Ce^{IV}(PW_{11})_2$.

Effect of pD



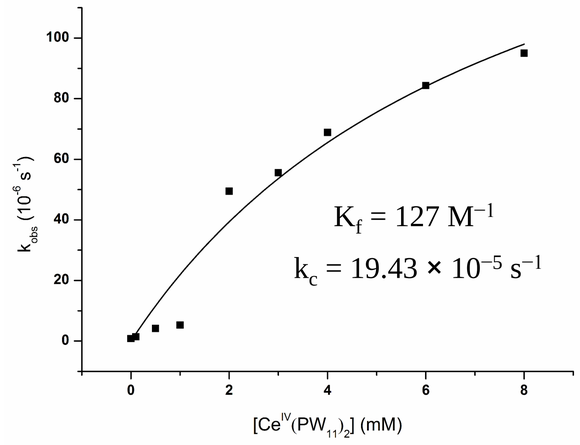
pD dependence of Δk_{obs} (the difference in k_{obs} for hydrolysis of 1.0 mM NPP with and without 1.0 mM $Ce^{IV}(PW_{11})_2$ at 50 °C).

Effect of temperature

E_a (kJ mol^{-1})	
With $Ce^{IV}(PW_{11})_2$	73.98
Without $Ce^{IV}(PW_{11})_2$	135.97

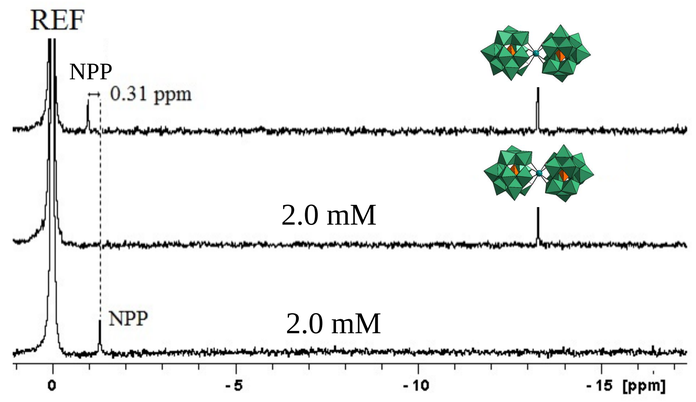
$\Delta^{\#}H$ (kJ mol^{-1})	$\Delta^{\#}S$ (J mol^{-1} K^{-1})	$\Delta^{\#}G$ (kJ mol^{-1}) 50 °C
71.14	-121.52	110.39

Effect of $Ce^{IV}(PW_{11})_2$ concentration



Dependence of $Ce^{IV}(PW_{11})_2$ concentration on the hydrolysis of 1.0 mM of NPP at pD 6.4 and 50 °C.

The interaction between NPP and $Ce^{IV}(PW_{11})_2$

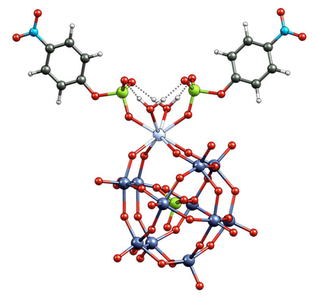


^{31}P spectra of 2.0 mM $Ce^{IV}(PW_{11})_2$, 2.0 mM NPP and their mixture at pD 6.4.

DFT calculation

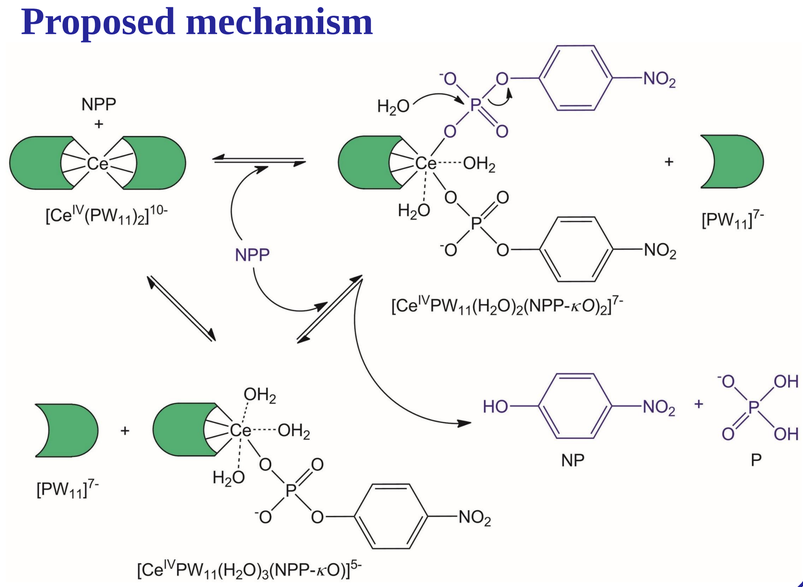
$[Ce^{IV}(PW_{11})_2]^{10-} + nH_2O + mNPP^{2-}$
$\rightarrow [Ce^{IV}PW_{11}(H_2O)_n(NPP)_m]^{(3+2m)-} + [PW_{11}]^{7-}$

➡ n = 2 and m = 2



DFT optimized complexes of $[Ce^{IV}PW_{11}]^{3-}$ with NPP.

Proposed mechanism



Conclusions and future work

- $Ce^{IV}(PW_{11})_2$ is stable under wide range of pD, initial POM concentration, temperature, and ionic strength. ^{31}P DOSY NMR showed that at very low pD, $Ce^{IV}(PW_{11})_2$ partially converts into the monomeric $Ce^{IV}PW_{11}$. These results facilitated detail kinetics and thermodynamic studies of NPP by this POM.
- DFT calculations confirmed that the presence of NPP may provoke dissociation of the parent POM $Ce^{IV}(PW_{11})_2 \rightarrow Ce^{IV}PW_{11} + PW_{11}$. NPP prefers to form complexes with the monomeric product $Ce^{IV}PW_{11}$ in the most stable complex $[Ce^{IV}PW_{11}(H_2O)_2(NPP\text{-}\kappa O)_2]^{7-}$.
- Further study will be focused on the hydrolytic activity of this POM towards RNA model substrate 2-hydroxypropyl 4-nitrophenyl phosphate (HPNP).

References

1. K. Stroobants, E. Moelants, H. G. T. Ly, P. Proost, K. Bartik, T. N. Parac-Vogt, *Chem. - Eur. J.*, **2013**, 19(8), 2848-2858.
2. T. K. N. Luong, P. Shestakova , T. T. Mihaylov, G. Absillis, K. Pierloot and T. N. Parac-Vogt, *Chem. Eur. J.*, **2015**, 21, 4428-4439.
3. T. K. N. Luong, T. T. Mihaylov, G. Absillis, P. Shestakova and K. Pierloot, T. N. Parac-Vogt, *Inorg. Chem*, **2016**, 55, 9898-9911.

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Certificate of attendance

We hereby confirm that

Thi Kim Nga Luong

attended the 19th Central and Eastern European NMR Symposium & Bruker Users' Meeting
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Bruker BioSpin, Germany

Prof. Dr. Eng. Corneliu-Mircea Davidescu
Vice-rector of University Politehnica Timisoara
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